which the present disclosure demonstrates - namely, that serotypes from the same subgroup can be combined in a series of adenovirus vectors, and that such vectors are not cross reactive when administered into a subject.

Election/Restriction

The Examiner's requirement for restriction, made final in the October 24, 2000 Office Action, is acknowledged. Claims 1-4, 8, 9, 13 and 14 remain pending in this application.

Priority

It is acknowledged that the Examiner stated that there is no support in parental applications, 09/251,955, 08/473,168, 08/250,885, or 08/080,727, for the claims in this application.

For the purposes of this response, the Applicants consider that priority is a non-issue because no claims stand rejected herein on the basis of prior art. Therefore, the Applicants present no counter-arguments to the Examiner's position, but reserve the right to respond to the priority matter at a later time. The Applicants do not accede to any asserted loss of priority for this application.

Specification

One change, reflecting the issuance of a patent, is made, as shown above.

35 USC § 112, Second Paragraph

Claims 1-4, 13, and 14 stand rejected under 35 U.S.C.112, second paragraph, as being indefinite based on specific phrases recited in claims 1 and 13.

With regard to claim 1, the meaning of "substantially devoid" derives from references in the specification as to improvements in the art, such as on page 2, line 27, ("deleted for most if not all viral coding sequences" which resulted in the qualities described on page 3, lines 2-3), and page 4, lines 11-12 and lines 17-18. These passages describe previous efforts at substantially reducing or eliminating the DNA sequences that encode adenoviral proteins. Another passage, page 19, line 21, through page 22, line 6, describes the activities conducted for the present application that achieved production of helper dependent Ad having no detectable Ad protein coding sequences. The Applicants believe that, based on these passages, the recited term, "substantially devoid" in claim 1 is sufficiently defined and is sufficiently clear in the disclosure as indicated herein.

Claim 13, as amended, *supra*, incorporates more definitive language and has eliminated the phrases objected to by the Examiner. Accordingly, it is believed that claim 1, and claim 13, as amended, overcome the Examiner's grounds for claim rejections under 35 USC § 112, first paragraph. Reconsideration and withdrawal of this ground for rejection is respectfully requested.

With regard to the bases for the rejections of claims 13 and 14 under 35 U.S.C. 112, second paragraph, it is noted for the record that the reasons for the amendments, to overcome the indefiniteness asserted by the Examiner, do not pertain to narrowing said claims for reasons related to a statutory basis of patentability. Rather, the amendments merely provide clearer language to define what the Applicants regard as their invention.

35 USC § 112, First Paragraph

Claims 1-4, 8, 9, 13, and 14 stand rejected under 35 U.S.C.§ 112, first paragraph, because the specification, although acknowledged as being enabling for Ad-2 and Ad-5, "does not reasonably provide enablement for making and using hdAd or helper adenoviruses encoding capsid proteins *from any and all adenoviral serotypes*." (Emphases added.) More generally, the Examiner states that the specification does not enable persons skilled in the art "to make the invention commensurate

in scope with these claims."

The Applicants respectfully offer the following discussion and argument to overcome the specific issues raised by the Examiner in rejecting these claims under 35 USC § 112, first paragraph.

Immunogenic advantages using closely related Ad-2 and Ad-5

On page 5 of the Office Action the Examiner notes that the Ad-2 and Ad-5 serotypes ". . . are from the same closely related subgroup . . .". This issue was raised to make a point that this example did not "reasonably provide enablement for making and using hdAd or helper adenoviruses encoding capsid proteins from any and all adenoviral serotypes." (Page 4). While the latter point is dealt with in the subsections below, this subsection discusses the immunological justification for, and advantages of, using the relatively closely related Ad2 and Ad5 serotypes, to enable this invention to the full scope of the claims.

Regarding the key immunological aspect of this invention, that a series of helper viruses of different serotypes will not induce cross-reactive antibodies in a recipient receiving serial administrations, it is axiomatic that the differing immunogenicity of different serotypes of helper adenoviruses is critical to the effectiveness of this invention. A key consequence of the Ad-2/Ad-5 closeness is the demonstration of the differing immunogenicity *even with relatively closely related serotypes*. That is, the present invention disclosure demonstrates that antibodies against recombinant hdAd5 vectors do not cross-react to neutralize an adenovirus comprising virion capsule protein components even from Ad-2, which is closely related to, and in the same subgroup C, as Ad5.

One result of this finding is the reasonable expectation that more widely divergent serotypes will not create antibodies cross-reacting with hdAd vectors bearing capsid proteins provided by helper viruses from more divergent sertotypes. This determination can be readily achieved for each contemplated combination of serotypes for a particular desired use, without undue experimentation,

by techniques disclosed in this application and known to those skilled in the art. For example, one method to assess the cross reactivity of antibodies to one serotype on a second serotype is disclosed in the application on page 24, lines 13-24.

This expectation is, to some extent, supported by speculation in the literature. Thus, for example, Mastrangeli et al. (Human Gene Therapy 7: 79-87, 1996), while experimenting on the concept of repetitive administrations of non-recombinant Ad vector to circumvent anti-Ad immunity in Cystic Fibrosis gene therapy, found that pre-immunization with one or more wild-type Ad (using one Ad from subgroups C, E and D), followed by a single administration of a replication-deficient recombinant vector derived from Ad5 serotype (subgroup C), resulted in effective expression from the Ad5 vector when D and E subgroups were the pre-immunizations (but not so for the wild-type C-group Ad). Based on these results, Mastrangeli et al. questioned whether repeat administrations using "recombinant Ad vectors based on *different Ad subgroups. . .*" might be effective. (p. 86, emphasis added).

This indicates a belief in, and a corresponding vison, of a yet-to-be-developed treatment regimen that would utilize Ad vectors only from different subgroups. The results shown in the present application demonstrate that this view is unnecessarily limiting, in that vectors having protein coats derived from even closely related serotypes from the same subgroup can be used in a sequential administration with little or no development of cross reactive antibodies, even when the helper viruses provide capsid proteins from the same adenoviral subgroup (C).

The applicants are adding new claim 15 to specifically claim the use of two or more serotypes from the same subgroup being used to provide capsid proteins in a series of adenovirus-based vectors made according to the present invention. Since the present disclosure provides direct evidence of the ability to circumvent immune responses between even closely related adenoviral vector serotypes from the same adenoviral subgroup, and since the literature provides circumstantial evidence that this same result might be achievable if and only if a successful schema for recombinant

vector construction including different capsid protein serotypes could be developed, those skilled in the art would be fully enabled by the present disclosure to construct both closely related and distant hdAd vectors.

Further evidence exists in the art that less closely related serotypes also do not induce cross-reactive antibodies. Kass-Eisler et al. (Gene Therapy 3:154, 1996) demonstrated that pre-immunization of mice with wild-type Ad7 (subgroup B) did not interfere with the ability of an Ad5-based vector (subgroup C) to efficiently transduce the mice and lead to transgene expression. In addition, pre-immunization of mice with wild-type Ad7 (subgroup B), followed by immunization with wild-type Ad4 (subgroup E), followed by delivery of an Ad5-based vector (subgroup C) did not inhibit the ability of the Ad5 vector to transduce and lead to transgene expression in these studies.

Also, producing an Ad vector with a hybrid coat-protein derived from Ad5 (subgroup C) and Ad12 (subgroup A) allowed the hybrid virus to escape neutralization by antibodies raised against Ad5, and allowed effective administration of the vector to mice even in the presence of Ad5 neutralizing antibodies (Roy J. Virol 72:6875, 1998). Thus, it is clear from the literature that viruses of different serotype, subgroup or species can be utilized to achieve successful re-administration of Ad vectors that overcome preexisting neutralizing antibody, whether naturally occurring or induced by a previous administration of a first serotype. This is true for viruses of different serotypes, but within the same subgroup (as disclosed in the present specification), as well as for viruses of different serotypes from different subgroups (as disclosed in the three references cited).

None of these cited references used helper/helper dependent systems to develop a series of hd vectors, where the series includes genetically identical hdAd vectors derived from helper adenoviruses having capsids of different serotypes. Nor did the references disclose sequential administration of such a vector series. Nor did the references demonstrate suitability of serotypes from the same subgroup as suitable for use in such a series.

As noted, the differences in immunogenicity are critical to the successful implementation of the present invention. Had the Applicants evaluated two adenoviruses that were remotely related, the question may have arisen as to whether more closely related serotypes would still be immunogenically distinct when applied to a subject sequentially. Given knowledge in the relevant art, this example sufficiently establishes that different serotypes, when used for the helper virus, are reasonably expected not to raise antibodies that are cross-reactive with other serotypes more divergent than Ad-2 and Ad-5. The serial administration of vectors having different serotypes, in accordance with the present invention, will result in the effective transfer of genetic material for a longer time than re-injection of the original serotype, thereby providing an advancement in the art in accordance with the claims.

Further, the claims are enabled even if, after experimentation with different serotype and HD vectors, some combinations are found inoperative. As the C.C.P.A has stated:

> As far as [applicant's] arguments go, they are persuasive. We agree that [applicant's] claims are not too broad "to the point of invalidity" just because they read on a large number of inoperative embodiments, since it seems to be conceded that a person skilled in the relevant art could determine which conceived but not-yet-fabricated embodiments would be inoperative with expenditure of no more effort than is normally required of a lens designer checking out a proposed set of parameters.

In re Cook, 169 USPQ 298, 302 (C.C.P.A. 1971). It is respectfully argued that the advanced state of knowledge and the level of typical experimentation in the art would allow the determination of operative and inoperative serotype combinations such as for the invention in *In re Cook*, without undue experimentation.

Further, in *The Johns Hopkins Univ. v. CELLPRO, Inc*, 152 F.3d 1342, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998), the Court stated:

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. (*quoting PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996))

The evidence provided herein shows that a person of ordinary skill in the art would have sufficient knowledge and expertise to follow the methods described and referred to in the specification, and to check different serotype combinations to find combinations that function together.

The Court in *Johns Hopkins* also expressed support for the lower court's negation of *CELLPRO's* argument that experts who could only produce antibodies after several attempts using *Johns Hopkins*' patented method was evidence of undue experimentation. The lower court, again quoting *PPG Indus.*, stated that "[r]outine repetition of a patent's specification to achieve a desired experimental result does not constitute undue experimentation." Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM, at 5 (D. Del. Feb. 24, 1997) (citing PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623-24 (Fed. Cir. 1996)). This also supports the Applicants' position that undue experimentation is not the proper characterization for the type of routine, albeit multi-step and sophisticated experimentation that is typical to this art, even when such experimentation requires repetition to obtain a suitable product or working system. These Federal Circuit statements apply not only to this sub-topic, but to the sub-topics discussed below.

Discussion regarding sufficient guidance for combining ITRs or Packaging Signals from different Serotypes

The Examiner, on page 5 of the Office Action, asserts that the specification does not provide sufficient guidance regarding "which adenoviral serotype ITRs or packaging signals can be complemented or recognized by which heterologous adenoviral capsid serotypes." Further, it is stated that such complementation would appear 'highly unpredictable' because (1) it is not routinely performed, and (2) there is no expectation of success "in mixing or matching any of the 40+ adenoviral serotype capsid and ITR/packaging site elements [from different subgroups] to form infectious particles . . .". While these statements clearly support the novelty and non-obviousness of the present invention as disclosed and claimed herein, the Applicants take these sentences to question 1) whether a particular helper Ad of a particular serotype can provide a compatible capsule for packaging genetic material from a different serotype, and 2) whether genetic modifications of ITRs and packaging signals in vectors would provide a suitable means to practice the invention with hAds and hdAds from different serotypes. A more detailed discussion of the compatibility of ITR/packaging signals with binding proteins of different serotypes is provided below, in a separate sub-section.

With regard to general aspects of the above statements, it is respectfully urged that encapsulation of adenoviral DNA generally will occur so long as (1) the DNA is not too large in size, and (2) that DNA includes an appropriate packaging signal. Even if some serotype combinations do not achieve the desired results, such as due to widely divergent HDAd ITR/packaging signals and helper Ad proteins, one of ordinary skill in the art could readily determine this based on routine, and not undue, experimentation. Also, it is within the capability of one of ordinary skill in the art at the time of filing to predict combinations more likely to provide a desired replication rate, and/or to produce helper and hd Ad that have matching, or at least compatible, ITR/packaging signals.

For instance, Roy et al. (J. Virol 72:6875, 1998) demonstrated that the ITRs and packaging signal of Ad5 (subgroup C) are compatible with capsid proteins of Ad12 (subgroup A). Thus Roy et al. have shown that a chimeric virus could be constructed from Ad5 and Ad12 that circumvents immunity against Ad5. Consequently, by following the methods taught in the present disclosure,

one skilled in the art could readily modify the virus of Roy et al. so that it could serve as a helper virus in the present invention. For example, this could be accomplished by rescuing a floxed packaging signal into their hybrid virus.

Furthermore, to the second question above, one does not need to utilize the same ITRs and packaging signal for all the vectors used in a series of treatments, and matching ITRs and packaging signals are obtained through routine genetic modification. The ITRs and packaging signals are *cis*-acting elements and have no real function in terms of ability of the virus to express the transgene. Thus, for example, the ITR and packaging signal for Ad12 have been identified and characterized. These could be cloned into a hdAd plasmid in place of or in addition to the Ad5 ITR and packaging signal. Thus, this vector would be easily replicated and packaged by an Ad12 helper virus (constructed in a similar manner to the Ad2 and Ad5 helper viruses disclosed in the present disclosure), but all of the internal characteristics of the vector (expression cassette, stuffer DNA, transgene) would be identical for all vectors used in the serotype switching strategy.

Support for such routine genetic manipulation is found in the specification, page 21, lines 7-17, and page 22, lines 27-28. Here, the construction of an Ad2-based helper virus started with a plasmid, pLC8c, having left-end ITR and packaging signal from Ad5 (see also Figure 2). The resulting Ad-2 based helper virus, Ad2LC8cCARP, contained Ad2 genomic material, including genes for the capsid proteins. This helper virus, when infected onto 293Cre cells after pRP1050 (an Ad5-based hd Ad vector), resulted in Ad2RP1050 (page 23, lines 21-28). As shown further in the specification, Ad2RP1050 provides the Ad5-based genetic material of pRP1050 and the Ad2 serotype capsid proteins, and does not cross react with Ad5-generated antibodies. This demonstrates a basic approach, with techniques known to those skilled in the art, to avoid potential difficulties matching ITRs and packaging signals. This approach can be used to prepare a series of hd vectors having non-cross reacting capsid proteins of different serotypes that coat a largely consistent viral genome containing one or more genes of interest for expression in cells.

Thus, from a technical standpoint, there is a reasonable expectation of success to combine many, if not most, serotypes where the helper Ad originates from one serotype and the hd-Ad originates from a different serotype. As indicated above, not all embodiments need be operative to provide an enabling disclosure. It is asserted that given the disclosure and knowledge in the art, as partly demonstrated by the references cited above, in combination with the disclosure and guidance provided in the present specification, many if not most efforts would result in operative embodiments, which could be identified through routine experimentation.

Correlation between tropism of Ad serotype groups and their ability to infect different cell types

The Examiner also raises the issue of tissue tropism on page 5 and 6 of the Office Action as a ground to support the 35 U.S.C. 112 enablement rejection. By tropism is meant that different adenoviruses typically invade specific groups of tissues. The Examiner questions the sufficiency of the specification as to teaching which serotype helper Ads can be interchanged to achieve an effective sequence of capsule proteins for a series of administrations directed to a particular cell type or range of tissues that are not the common sites of infectivity. Although the Applicants do not dispute the scientific findings in the cited Bailey et al., Hay, and Temperley et al. articles, they decidedly view these findings as neither representing or predicting the actual capacities of different serotypes to invade cells not of the 'specified tropism' shown in the Bailey et al. Table 2 (page 440).

First, the Bailey et al. article is directed to phylogenetic studies, not to actual experiments regarding the ability of different serotypes from different subgenera to invade a specific cell type. More importantly, as the table heading specifies, the sites of infection listed are "Common Site(s) of Infection." (Emphasis added.) It is not disputed that the binding efficiency toward other sites *may*

be less, or the defense mechanisms of other cell types *may* be greater for a particular serotype. The critical point is that a particular Ad from a serotype with a 'common' site of infection is able to invade other cell types. The latter is critical because, *inter alia*, the dosage and choice of specific serotypes for a particular application can be adjusted to compensate for the binding efficiency and defense factors.

The following references substantiate the knowledge in the art of broader infectivity for Ad2 and Ad5 than suggested by Table 2 of Bailey et al.:

1. It is well known that Ad5 and Ad2 vectors can deliver genes to liver (*cf* Kay, M. A., Graham, F. L., Leland, F. and Woo, S. L. C. Therapeutic serum concentrations of human alpha-1-antitrypsin after adenoviral-mediated gene transfer into mouse hepatocytes. Hepatology 21: 815-819, 1995).
2. Ad5 and Ad2 vectors also are known to deliver genes to spleen, liver, kidney, lung (cf Fig. 6 and Table 1 of Mittal, S. K., McDermott, M. R., Johnson, D. C., Prevec, L., and Graham, F. L. Monitoring foreign gene expression by a human adenovirus based vector using the firefly luciferase gene as a reporter. Virus Research 28: 67-90, 1993).
3. Ad5 and Ad2 vectors also are known to deliver genes to liver, lung and heart (Figure 6 of Kass-Eisler et al. Gene Therapy 3:154, 1996; and Kass-Eisler et al. Proc. Natl. Acad. Sci USA 90: 11498-11502, 1993).
4. In Quantin et al. Proc. Natl. Acad. Sci. 89:2581-2584, a recombinant Ad-5 virus successfully invaded muscle cells in mice. It is noted that muscle cells are not included as "Site(s) of infection" on Table 2 of Bailey et al.

Further, a more comprehensive list of cell types and tissues that can be transduced by adenovirus vectors is given in Table 1 of Hitt, M., Addison, C. and Graham, F.L. Human adenovirus vectors for gene transfer into mammalian cells. In: "Advances in Pharmacology - Gene Therapy" Ed. J. Thomas August, Academic Press. San Diego, CA. 40: 137-206, 1997.

Accordingly, it is well known in the art that adenoviruses infect tissues other than those listed as "Common Sites" in Bailey et al., and in particular, adenovirus vectors have been used extensively to deliver and express genes in a wide variety of tissues. The Applicants believe that the Examiner has improperly concluded from a phylogenetic paper's general overview of 'common' sites of infection that Ads from a particular serotype can only invade cells of that serotype. The Applicants will provide additional references countering this conclusion if so requested by the Examiner.

In conclusion, regarding the tropism-based non-enablement ground for rejection raised by the Examiner, the tropism and relative infectivity of many Ad serotypes were known in the art at the time of filing this application. For a particular application of the present invention, any information not known in the art could be readily determined by routine methods known to those of ordinary skill in the art without undue experimentation based on the teachings of the present disclosure. In this way, or by using knowledge already available in the art, a suitable sequence of helper Ad serotypes could be readily determined for a specific application. This level of additional experimentation is routine and does not render the specification non-enabling. Accordingly, reconsideration and withdrawal of this ground for rejection is respectfully requested.

Ability of trans packaging factors and cis packaging signals from different serotypes or subgenera to function together

The Examiner also raises, as a ground for the 35 U.S.C. 112 enablement rejection, the ability of trans packaging factors and cis packaging signals from different serotypes or subgenera to function together. The Examiner is referred to the section above, "Discussion regarding sufficient guidance for combining ITRs or Packaging Signals from different Serotypes," for information that also applies to the current section.

Starting on the last line of page 6 of the Office Action, the Examiner provides information from Thorner et al., Hearing et al., and Klimkait et al. regarding scientific data that shows differences in

the structure, and in some cases the performance, of Ad packaging signals of differing serotypes and proteins that activate them. The Examiner then concludes with the statement that, "these observations suggest the unpredictability associated with mixing and matching adenoviral *cis* and *trans* functions from different serotypes in the absence of trial and error experimentation requiring undue experimentation." (Underline added for emphasis.)

The Applicants concur that the scientific literature in this art has shown certain incompatibilities among serotypes regarding how well *trans* proteins from a different serotype function with a particular *cis* packaging signal. However, this knowledge properly leads to two conclusions:

1. One of ordinary skill in the art is aware of these differences in compatibilities and, in some cases, has knowledge of reported differences in efficiency and the effect of host cell proteins such as NF1. With this knowledge, one of ordinary skill in the art can derive the critical teaching from the Applicants' specification and, without undue experimentation, devise an appropriate sequence of helper Ads to function sufficiently well with a particular hdAd. Further, modifications to either helper or hd genome can be achieved by methods well known in the art to improve the performance and compatibility of a particular combination of helper and hdAds of different serotypes. The referenced papers, and subsequent papers listed in the IDS filed by the Applicants on June 2, 1999, demonstrate that these techniques were well known and can be readily utilized in routine experimentation.

2. A lower replication rate, such as that reported in Hay (e.g., page 135), does not lead to the conclusion that the Applicants' specification is not enabling. It merely indicates that some combinations will be more effective than others, and suggests that dosages may need to vary, partly based on the differences in replication due to relative lower inefficiencies such as those reported. Teachings to obviate or overcome this possible effect are not required to enable the invention when the knowledge is available in the art and no claim is made to attaining a specific replication rate for all serotype combinations or a minimum dose/response effect.

Thus, although the cited references provide data that *suggest* a difficulty in the routine practice by those of ordinary skill in the art, these and other references inform those skilled in the art of possibly lower replication efficiency with some serotype combinations, and suggest ways to avoid or overcome them. Therefore, although the Examiner cites Bailey et al. to support the statement "such Ad functions [of helper Ads of different serotypes than the hdAd] are not interchangeable," methods are known to overcome such incompatibilities. In particular, genetic recombination, very well known in the art, can be used to match the genes in a hAd that express proteins binding to the ITRs and packaging signals to those particular ITRs and packaging signals in the hdAd in use in a particular series.

Also, as stated, *supra*, page 8, the same ITRs and packaging signal for all the vectors used in a series of treatments need not be identical. These are only *cis*-acting elements and have no real function in terms of ability of the virus to express the transgene. For example, the ITR and packaging signal for Ad12 have been identified and characterized. These could be cloned into a hdAd plasmid in place of the Ad5 ITR and packaging signal. This vector would be easily replicated and packaged by an Ad12 helper virus (constructed in a similar manner to the Ad2 and Ad5 helper viruses disclosed in the present disclosure), but all of the internal characteristics of the vector (expression cassette, stuffer DNA, transgene) would be identical for all vectors used in the serotype switching strategy.

Further, as noted, dosages may be modified to improve the output of sub-optimal combinations. Accordingly, reconsideration and withdrawal of this ground for rejection is respectfully requested.

<u>Concluding remarks regarding enablement of helper Ad combining with hd-Ad, where both are from "any and all adenovirus serotypes"</u>

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988), *cert.*

denied, 490 U.S. 1046 (1989). A patent need not teach, and preferably omits, what is well known in the art. *See* M.P.E.P., § 2164.01. When considering the undue experimentation factors, the Examiner's analysis "must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole." *See* M.P.E.P., § 2164.01(a).

Based on the foregoing facts and law, it is respectfully urged that the Applicants have provided sufficient facts well known in the art at the time of filing this application to demonstrate enablement commensurate with the breadth of the claims. Specifically, considering the present disclosure and the direction provided therein, the knowledge and level of ordinary skill in the art, the predictability of experiments in the art, the typical level of routine experimentation that is not considered 'undue' in this art, and the nature of the invention and breadth of its claims, the making and using of the Applicants' invention was readily attainable by those of ordinary skill in the art. Therefore, considering the evidence as a whole as it relates to all factors, it is respectfully maintained that a proper analysis in light of the information provided herein leads to a conclusion of enablement for the claims as provided and amended.

Drawings Objections

The Draftsperson objected to margins, character of lines, numbers and letters, and size of numbers, letters and reference characters in the drawings. These objections will be addressed and overcome by filing formal drawings prior to or upon receipt of a Notice of Allowance in this case.

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All grounds for rejection or objection having been addressed and overcome herein, it is respectfully urged that this application is in condition for allowance. Should the Examiner be of the opinion that there remain valid grounds on which any of the claims as herein amended may be rejected, it is respectfully requested that the undersigned be accorded the courtesy of a telephonic or in-person

interview to address and overcome any such remaining grounds for rejection.

Respectfully submitted,

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Versions of Rewritten Specification and Claim to Accompany Applicants' April 24, 2001 Response to Office Action, Paper No. 8

In the Specification, replace the paragraph beginning on page 16, line 28, and ending on page 18, line 3, with the following paragraph:

There are many known ways to construct adenovirus vectors. As discussed above, one of the most commonly employed methods is the so called "two plasmid" technique. In that procedure, two noninfectious bacterial plasmids are constructed with the following properties: each plasmid alone is incapable of generating infectious virus. However, in combination, the plasmids potentially can generate infectious virus, provided the viral sequences contained therein are homologously recombined to constitute a complete infectious virus DNA. According to that method, typically one plasmid is large (approximately 30,000-35,000 nt) and contains most of the viral genome, save for some DNA segment (such as that comprising the packaging signal, or encoding an essential gene) whose deletion renders the plasmid incapable of producing infectious virus. The second plasmid is typically smaller (eg 5000-10,000 nt), as small size aids in the manipulation of the plasmid DNA by recombinant DNA techniques. Said second plasmid contains viral DNA sequences that partially overlap with sequences present in the larger plasmid. Together with the viral sequences of the larger plasmid, the sequences of the second plasmid can potentially constitute an infectious viral DNA. Cotransfection of a host cell with the two plasmids produces an infectious virus as a result of homologous recombination between the overlapping viral DNA sequences common to the two plasmids. One particular system in general use by those skilled in the art is based on a series of large plasmids known as pBHG10, pBHG11 and pBHGE3 described by Bett, A. J., Haddara, W., Prevec, L. and Graham, F.L: "An efficient and flexible system for construction of adenovirus vectors with insertions or deletions in early regions 1 and 3," Proc. Natl. Acad. Sci. US 91: 8802-8806, 1994 and in US patent application S/N 08/250,885, now issued as U.S. Patent No. 6,140,087, and published as WO95/00655

(hereby incorporated by reference). Those plasmids contain most of the viral genome and are capable of producing infectious virus but for the deletion of the packaging signal located at the left end of the wild-type viral genome. The second component of that system comprises a series of "shuttle" plasmids that contain the left approximately 340 nt of the Ad genome including the packaging signal, optionally a polycloning site, or optionally an expression cassette, followed by viral sequences from near the right end of E1 to approximately 15 mu or optionally to a point further rightward in the genome. The viral sequences rightward of E1 overlap with sequences in the pBHG plasmids and, via homologous recombination in cotransfected host cells, produce infectious virus. The resulting viruses contain the packaging signal derived from the shuttle plasmid, as well as any sequences, such as a foreign DNA inserted into the polycloning site or expression cassette located in the shuttle plasmid between the packaging signal and the overlap sequences. Because neither plasmid alone has the capability to produce replicating virus, infectious viral vector progeny can only arise as a result of recombination within the cotransfected host cell. Site-specific methods for achieving recombination may also be employed when practising the present invention.

Replace claim 13 as follows (marked-up version):

Claim 13 (Amended):

13. A method of making a series of genetically identical adenoviral vectors wherein each member of said series has a different serotype, for delivering and expressing a desirable gene in a recipient of said series of genetically identical adenoviral vectors which comprises:

(a) making a series of helper adenoviruses of differing serotypes, each serotype of said series of adenoviruses expressing a different set of capsid proteins;

(b) making a helper dependent adenovirus vector, hdAd, having a genome encoding said gene, an adenoviral packaging signal, the adenoviral left ITR and the adenoviral right ITR and as much additional nucleic acid sequences as are necessary to ensure [efficient] expression of said gene and [efficient] packaging of said hdAd genome, but encoding little or no adenoviral gene products;

(c) generating a first stock of said hdAd *in vitro* by co-introducing into a cell said hdAd genome and a helper adenovirus of a first serotype under conditions whereby little or [essentially] no infectious particles of helper virus are present in the final hdAd stock, but wherein said stock is highly enriched in infectious particles comprising said hdAd genome and capsid proteins encoded by said helper adenovirus of said first serotype;

(d) repeating step (c) as many times as desired using a helper adenovirus of a different serotype each time said step (c) is repeated, such that a series of infectious hdAd stocks are generated, with each said stock having [a] said different set of capsid proteins based on said [of] different serotype; and

(e) recovering said infectious hdAd stocks having a capsid of different serotype to obtain said series of genetically identical adenoviral vectors.